Neural Correlates of Emotion Regulation in Multiple Sclerosis

Research Thesis

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Abstract

Cognitive reappraisal is considered an adaptive emotion regulation strategy, involving the reinterpretation of negatively valenced stimuli. This process of reappraisal is thought to be cognitively demanding and is accompanied by increased recruitment of executive control regions and reduced activation in emotion-generating regions of the brain. However, there are few studies examining the neural correlates of reappraisal in populations with chronic medical illnesses, such as individuals with multiple sclerosis (MS), who experience greater emotion dysregulation and higher rates of cognitive impairment than the general population. This study investigated the associations between cognitive capacity, measured using the WAIS-IV Working Memory Index, and neural and behavioral correlates of reappraisal in 38 participants (ages 30-59) diagnosed with relapsing-remitting MS. Participants completed an emotion regulation task in the MRI, where they were asked to use reappraisal or simply observe negative or neutral health-related images. When viewing negative compared to neutral images, participants reported higher negativity ratings and were less successful at suppressing regions of the default-mode network, likely representing internal mentation in response to the images. Implementation of reappraisal resulted in significant downregulation of negative emotions and activation of regions frequently observed in previous studies of healthy adults, including inferior and superior frontal gyrus and dorsolateral prefrontal cortex (dlPFC). Interestingly, during reappraisal, those with greater cognitive capacity exhibited more recruitment of the dlPFC, which in turn was associated with reappraisal success. These results suggest that better cognitive functioning in individuals with MS is linked to more successful implementation of cognitive reappraisal.

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Introduction

Multiple sclerosis (MS) is the most common neurological disease in young adults (see Calabrese, 2006 for review). MS is associated with deficits in both cognitive and emotional functioning (Bobholz & Rao, 2003; Calabrese, 2006). Despite the relatively high prevalence of this neurological disease in young adults and its significant impact on psychiatric health, there is limited research aimed at understanding the behavioral and neural correlates of problems with emotion regulation in this population. It is theorized that emotion regulation is more difficult for individuals with chronic illnesses, such as people with MS (PwMS; Phillips et al., 2014), when the illness produces deficits in cognitive function, as it has been hypothesized that executive functioning subserves successful emotion regulation (Gross 2002; Ochsner & Barrett 2001). Specifically, lower cognitive abilities may limit the extent to which individuals can successfully implement regulation strategies, such as cognitive reappraisal, that place high demands on cognitive processes (Phillips et al., 2014). Therefore, the current study explores how cognitive function in a sample of PwMS is related to successful use of a cognitively demanding emotion regulation strategy, cognitive reappraisal, at the behavioral and neural level.

Multiple Sclerosis

MS is a chronic neurodegenerative disease, associated with a wide range of heterogeneous physical and cognitive symptoms. Individuals with this inflammatory condition develop multiple areas of axonal demyelination, with these lesions often occurring in the deep white matter of the frontal lobes (Brownell & Hughes, 1962). MS is the leading cause of neurological disability for adults between 20 and 50 years old (Rouleau et al., 2017), with more

than 2.3 million people effected worldwide (National MS Society, 2017). There are four distinct subtypes of MS. This study focuses on relapsing-remitting multiple sclerosis (RRMS) as it is the most common subtype, accounting for 85% of diagnoses (National MS Society, 2017). RRMS is described as having periods of exacerbations that recede, followed by periods where there is no disease progression or worsening (Arnett, Meyer, Merritt, & Strober, 2018).

Common symptoms of this disease include overwhelming fatigue, problems with sensation, and difficulties with mobility (Arnett, Meyer, Merritt, & Strober, 2018). Along with these physical challenges, MS is also associated with impacting cognitive domains (Prakash, Snook, Lewis, Motl, & Kramer, 2008), including, but not limited to, declines in attention (Roth, Denney, & Lynch, 2015), memory (Rouleau et al., 2017), and emotion regulation (Phillips et al., 2014; Wierenga, Lehto, & Given, 2017). Previous studies have suggested that deficits in processing speed (Phillips et al., 2014) and working memory capacity (Parmenter et al., 2006) observed in PwMS, may contribute to the higher levels of affective symptoms.

Emotion Regulation

Emotion regulation and emotion generation are thought to involve similar cognitive and neural processes (Kappas, 2011; Mesquita & Frijda, 2011). However, it is useful to conceptually separate them to better understand emotion regulation. The generation of emotions is thought to occur through a Perception-Valuation-Action (PVA) sequence (Etkin, Büchel & Gross, 2015). This sequence involves three steps: (1) the brain perceives a stimulus from the individual's environment, (2) the stimulus is evaluated as containing a positive or negative valence (usually subconsciously), and (3) the positive or negative perception decision elicits an emotional response often causing a behavioral expression (i.e. smiling or crying) of the emotion (Etkin,

Büchel & Gross, 2015; Buhle et al., 2013). Emotion regulation refers to the process of managing our perception of, and response to an emotionally eliciting stimulus, with the goal of up- or down-regulating either the magnitude or duration of the emotional response (Gross, Sheppes, & Urry, 2011). One central aim of research in this area is to understand how emotion regulation lessens emotional distress, through altering emotion generation and reactivity.

In this vein, Gross (1998) released a model outlining the temporal steps taken during the regulation of emotional experiences. Once a regulation goal has been activated, various processes are engaged, including steps that modify attention, cognition, and emotional responses (Gross, 1998). Emotion regulation strategies can be employed at any point of response generation, and therefore have different consequences depending on which point of the generation cycle the strategies affect (Gross & Thompson, 2007).

Among the several emotion regulation strategies that impact the different stages of Gross' model, cognitive reappraisal is one of the most commonly researched. Cognitive reappraisal involves changing one's interpretation, or appraisals, of a stimulus (Buhle et al., 2013). This strategy has been found to decrease the experience of negative emotions and increase the experience of positive emotion (Gross, 2002; Gross & Thompson, 2007), suggesting that it is an adaptive strategy. Reappraisal is thought to require high levels of executive functioning (Opitz, Gross, & Urry, 2012; Goldin et al., 2008), suggesting that it is a cognitively demanding strategy. PwMS experience greater problems with successful emotion regulation than healthy controls (Phillips et al., 2014), possibly due to MS-related cognitive deficits.

It is important to understand affective functioning in the MS population, because emotion regulation ability has been shown to predict quality of life in healthy populations (Gross & John, 2003) as well as in PwMS (Phillips et al., 2009). Successful use of adaptive strategies, such as

cognitive reappraisal, has been associated with lower rates of psychopathology (Aldao, Nelen-Hoeksema & Schweizer, 2010) and better life adjustment in PwMS (Dennison, Moss-Morris, & Chalder, 2009). These results suggest an important role of successful use of adaptive strategies in the affective health of PwMS. Despite the elevated rates of emotion dysregulation in PwMS compared to healthy adults (Schirda, Nicholas, & Prakash, 2015; Prakash et al., under review), it has been shown that there is no difference in use of adaptive versus maladaptive strategies between PwMS and healthy controls (Prakash et al., under review). This suggests that affective dysfunction in PwMS may not be primarily driven by differences in the types of emotion regulation strategies used but may instead be related to the success with which they are able to implement adaptive strategies.

Some suggest that there is a possible link between deficits in executive functioning and decreased abilities to regulate emotions in PwMS. Although this has not been fully explored, poorer performance on a Go/No-Go and the FAS letter fluency task has been associated with higher scores on a measure of perceived emotion dysregulation – the Difficulties in Emotion Regulation Scale (Phillips et al. 2014). It has also been shown that cognitive deficits progressively compromise affective functioning in PwMS as the disease worsens (Amato et al., 1995).

The most common cognitive deficits observed in PwMS are working memory (Bobholz & Rao, 2003) and processing speed (see Chiaravalloti & DeLuca, 2008 for review). Working memory capacity refers to an individual's ability to hold and manipulate relevant information over time in the face of competing or cognitively demanding tasks (Conway et al., 2005). In order to change an interpretation of a negative stimulus, it is necessary to replace the negative thoughts with more adaptive (neutral or positive) thoughts. In healthy samples, those with higher

working memory capacity have been found to report lower levels of negative emotion during a reappraisal task (Schmeichel &Demaree, 2010), suggesting that they were better able to successfully down-regulate their emotional response using reappraisal. Additionally, an increased ability to update information in working memory has also been found to moderate the relationship between successful reappraisal and decreased negative emotions (Schmeichel, Volokhov, & Demaree, 2008; Pe, Raes, & Kuppens, 2013). Within PwMS specifically, problems with affective functioning have been linked to cognitive functioning, such that those who had depression and mood disorders performed worse on working memory and processing speed tasks (Chiaravalloti et al.,2005). These results indicate that working memory may play a significant role in facilitating the use of cognitive reappraisal, suggesting that MS-related deficits in working memory may be a key risk factor for affective dysfunction. Therefore, this study aims to investigate whether there is a link between cognitive function and the successful use of cognitive reappraisal in this population.

Neural Correlates of Emotion Regulation

The literature suggests that reappraisal is not a singular process, but a family of inter-related regulatory processes. Therefore, it is useful to employ a multi-modal approach to investigate these regulatory processes given evidence of shared neural circuitry underlying top-down cognitive processing and emotion regulation (see Oscher & Gross, 2008 for review). Functional Magnetic Resonance Imaging (fMRI) is a tool that has been commonly used to explore the neural mechanisms that underlie reappraisal and cognitive control. Evidence that cognitive reappraisal and cognitive control are closely interrelated comes from a body of neuroimaging

work showing that the two processes are associated with recruitment of several overlapping regions (see Oschner & Gross, 2005 for review).

Across two meta-analyses, the reappraisal process was consistently correlated with activation in several brain regions that are considered part of the executive control network. Specifically, use of cognitive reappraisal was associated with activity in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortices (dlPFC), and regions of the lateral fronto-parietal cortices (Buhle et al., 2013; Etkin, Büchel, & Gross, 2015). Reappraisal is thought to be a top-down cognitive process, recruiting both the prefrontal cortex and the ACC to modulate emotional responding by downregulating emotion generation regions, such as the amygdala and insula (Oschner & Gross, 2005; Oschner & Gross, 2008). Specifically, the dlPFC has consistently been shown to play a large role in reappraisal during both neutral and negative images (Golkar et al., 2012; Oschner & Gross, 2005), suggesting that this region is important in initiating the processes necessary for successful regulation. These results indicate that these cognitive capacity regions are integral for successful downregulation of negative emotional experiences through cognitive reappraisal.

Many studies have supported an overlap in neural recruitment between cognitive reappraisal and cognitive capacity. In fact, cognitive control has been implicated with increased activation in the PFC and ACC in healthy adults (Oschner & Gross, 2005), similarly to cognitive reappraisal. Specifically, the ACC has regularly been shown to play an important role in allocating cognitive resources during cognitively demanding tasks (Gennari et al., 2018), and it is thought to be activated early on in the emotion regulation process during the interpretation of incoming stimuli (Oscher & Gross, 2005). It also has been shown to play a role in monitoring control processes that have been associated with cognitive reappraisal (Oschner & Gross, 2008).

Self-control processing, however, is subject to fatigue and is largely reliant on an individual's cognitive capacity (Vohs & Heatherson, 2000). Higher cognitive capacity, specifically in working memory, has been associated with greater activation of the PFC during reappraisal tasks (Oschner & Gross, 2008). This is an important facet to note due to the cognitive deficits, particularly in working memory, commonly observed in PwMS (Parmenter et al., 2006), suggesting that there may be a relationship between cognitive capacity and problems with emotion regulation.

The interrelated neural processes of cognitive capacity and reappraisal found in healthy adults are also present in PwMS. The dlPFC was found to be recruited more during cognitively challenging tasks, specifically during a flanker inhibition task and a selective attention task, in PwMS (Prakash et al., 2008). PwMS also recruited the PFC and temporal lobe during a demanding working memory task (Hillary et al., 2003). This suggests that, similar to healthy adults, PwMS require increased recruitment of executive control regions in order to perform better on demanding tasks. Individual degree of cognitive capacity, similarly in healthy adults, was found to affect performance during working memory tasks; PFC activation differences were greater in PwMS who had cognitive deficits compared to PwMS without deficits or a healthy control (Chiaravalloti et al., 2005). With respect to lateral activation during demanding tasks, healthy controls were shown to activate the left PFC, while PwMS exhibited increased activation of the right and left PFC (Chiaravalloti et al., 2005). One explication of this difference would be that PwMS require bilateral PFC activation in order to perform better on the active task due to cognitive deficits associated with the MS disease (Parmenter et al., 2006). These results suggest that there are very similar neural activation patterns associated with working memory capacity in PwMS and healthy adults. This also could potentially speak to how declines in cognitive

function would require more recruitment of theses executive functioning regions to perform as well as healthy adults, leading to more fatigue due to the increased amount of resources used.

Although much is known about the neural correlates of working memory in MS, there is very limited research focused on exploring the neural correlates emotion regulation in this population. Together, these neuroimaging findings, in combination with the behavioral findings, provide strong evidence that top-down cognitive control and reappraisal are closely connected. These studies also speak to how the possible deficits in cognitive functioning could play a large role in affective symptoms and declines in successful affective functioning in PwMS. The current research will use MRI methods to examine the neural correlates of emotion regulation in MS in a grander attempt to explore the relationship between cognitive capacity and cognitive reappraisal.

Present Research

This study aims to investigate the neural correlates of cognitive reappraisal in individuals with MS. It will also explore the relation between behavioral and neural responses during cognitive reappraisal and investigate the correlations between cognitive capacity and successful regulation. Our hypotheses are guided by three specific aims:

1. **To examine behavioral and neural responses to a novel set of negative health-related images.** As this is a validation check of the manipulation, we expected to see higher reported levels of negative affect while individuals viewed negative health-related images compared to neutral images. Neurally, we expected to see increased activation in regions that are associated with emotion generation including areas of the limbic system, such as the amygdala and the cingulate gyrus.
2. **To determine the behavioral and neural correlates of cognitive reappraisal use in response to negative health-related images.** We hypothesized a reduction in negativity ratings when negative images were reappraised compared to observation-only trials. Neurally, we expected to find a reduction in amygdala activation and greater recruitment of executive control regions, like the ventromedial prefrontal cortices and lateral fronto-parietal cortices (Etkin et al., 2015) when participants were instructed to reappraise compared to observe negative images
3. **To examine the association between cognitive capacity and behavioral and neural indices of reappraisal use.** Considering individual differences in cognitive capacity, indexed by working memory, we expected those with lower cognitive capacity to show less reappraisal success. We also predicted a relationship between lower cognitive capacity and less recruitment of neural regions of interest associated with reappraisal success in

previous studies, including the ventral anterior cingulate, ventromedial prefrontal cortices, and the lateral fronto-parietal cortices Finally, we hypothesized that greater recruitment of these executive control regions that have been associated with enhanced reappraisal abilities will be related to greater success (i.e., reductions in negative emotion following reappraisal).

Method

Participants

Forty-four participants (8 Males; 36 Females; mean age = 45.80 years; SD = 8.01 years; mean education = 16.15 years; SD = 2.42 years) diagnosed with relapsing-remitting MS (mean disease duration = 11.32 years; SD = 8.28 years) were enrolled in the study. These participants were right handed, with 20/40 visual acuity or better. Those with a score higher than 19 on the Beck Depression Inventory (Beck, Steer, & Brown, 1996) and/or a score below 23 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) were excluded. Participants were excluded if they endorsed being diagnosed with comorbid psychological or neurological disorders. Participants were assessed for MRI safety by screening for metallic implants, prostheses, infusions, and invasive surgeries that are contraindicated to the MR environment (Table 1). Five participants were excluded due to MRI ineligibility. One participant was excluded due to scanner error during the emotion regulation task resulting in a loss of behavioral data. Thirty-eight participants (8 Males, 30 Females; mean age = 46.26 years; SD = 7.46 years; mean education = 16.38 years; SD = 2.40 years; mean disease duration = 11.48; SD = 8.52 years) were included in the final analysis (Table 2).

Table 1

Inclusionary criteria for enrollment in the present study

Right handed
Corrected vision ≥ 20/40
≤ 19 on the Beck Depression Inventory (Beck, Steer, & Brown, 1996)
> 23 or above on the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975)
0 ≤ Expanded Disability Status Scale ≤ 5.5 (Kurtzke, 1983)
Clinically diagnosed with RRMS
Relapse and corticosteroid free for the last 30 days
Absence of comorbid psychological or neurological disorders
Suitable to MR environment

Table 2

Participant characteristics for 38 adults (30 females; 8 males)

Variable	Mean (Standard Deviation)	Range
Age (years)	46.26 (7.46)	30-58
Education (years)	16.38 (2.40)	12-23
Disease Duration (years)	11.48 (8.52)	0.25-35
Expanded Disability Status Scale (EDSS)	3.79 (1.11)	0-5.5
Working Memory Index (WMI)	104.34 (15.76)	69-136

Measures/Procedures

Emotion Regulation Task

We employed a computerized emotion regulation task to measure behavioral and neural responding during cognitive reappraisal of negative health-related images. There were three conditions of the task: 1) Affect Regulate (AR) trials in which participants were asked to reappraise negative images, 2) Affect Observe (AO) trials in which they were asked to simply observe negative images, and 3) Neutral Observe (NO) trials in which they were asked to observe neutral images. Prior to entering the MRI scanner, participants were provided a description of cognitive reappraisal and how it can be used to regulate, or decrease, negative emotions. They then completed several practice trials during which they were asked to describe how they were using reappraisal in response to the example image out loud. Experimenters provided corrective feedback when necessary to ensure participants' abilities to employ the strategy. Participants then completed three runs of the experimental task in the MRI scanner (Figure 1).

Each of the three runs lasted approximately eight minutes, consisting of 18 trials (six AR trials, six AO trials, six NO trials). Each trial began with the presentation of a fixation cross (ITI = 4,000 ms or 7,000 ms) followed by a cue word (2,000 ms) instructing participants to either

"Observe" or "Reappraise" the upcoming image. This was followed by another fixation cross (4,000 ms) considered an anticipatory period. Participants were then presented with a health-related image that was either neutral or negatively valanced and implemented the cued behavior (8,000 ms). After viewing each image, participants saw a fixation cross (ITI = 4,000 ms or 7,000 ms) and then were asked to subjectively rate the amount of negative emotions they felt at the end of the viewing period on a 4-point Likert scale (1= not negative at all to 4= very negative). The behavioral dependent variables of interest were mean negativity ratings for each of the trial types (i.e., AR, AO, and NO) and reappraisal success calculated as the difference in mean negativity ratings following observation vs. reappraisal of negative images (AO-AR).

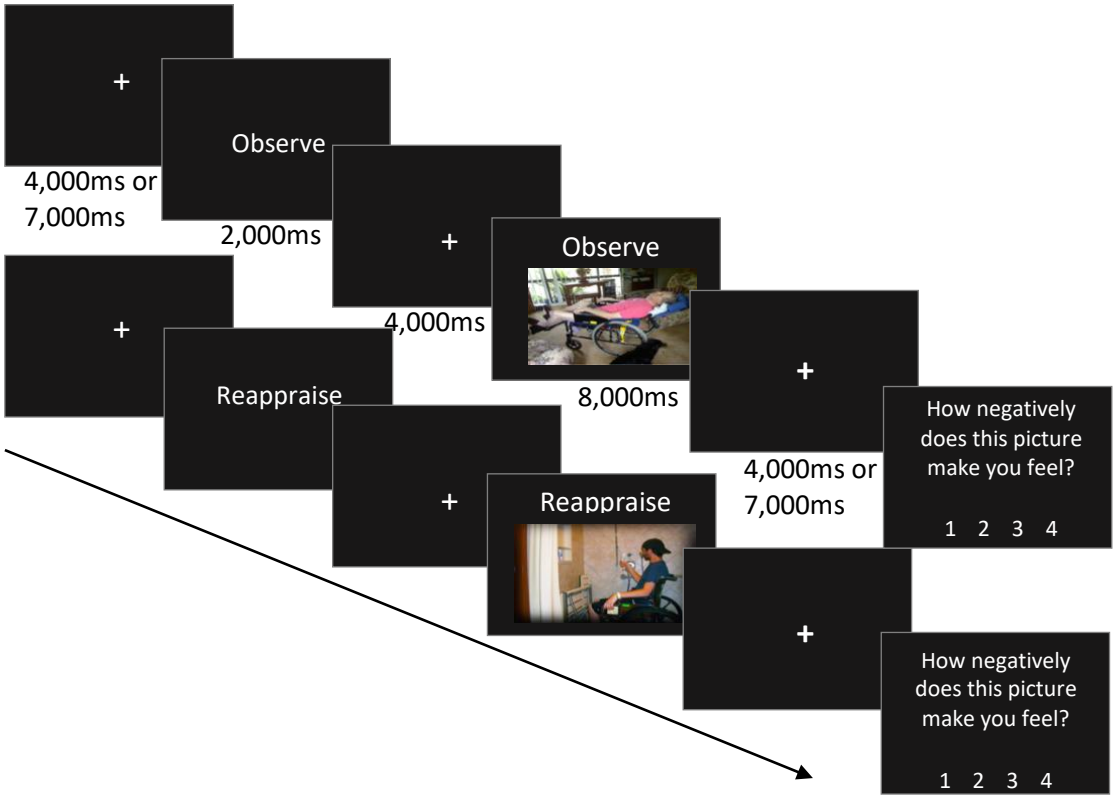

Figure 1. Schematic depiction of Emotion Regulation task trials. Participants completed a total of 54 trials separated into three runs of 18 trials each.

Working Memory Index

The Working Memory Index (WMI) from the Weschler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008) assesses the capacity to mentally manipulate information. The dependent variable was the age-corrected, standardized WMI score, calculated from the Digit Span and Arithmetic subtests.

The first subtest, Digit Span, measures working memory, manipulation, rote memory, learning, attention, and encoding through three different conditions. For Digit Span Forward, the participant was read a sequence of numbers and they were asked to repeat them back in the same order as they were heard. For Digit Span Backward, the participant was read a sequence of numbers and they were asked to recall them in the backwards order. For Digit Span Sequencing, the participant was read a sequence of numbers and they were asked to repeat them in order, starting with the lowest number. For scoring, one point is given for every correct trial and zero points are given for incorrect trails. Administration of each condition ended after two consecutive incorrect trials. The sum of correct trials was then used to calculate the scaled score for Digit Span.

The second subtest, Arithmetic, measures manipulation, concentration, attention, and numerical reasoning ability. The participants were asked to mentally solve a series of arithmetic word problems that were read aloud to them, with a time limit of thirty seconds for each trial. For scoring, one point is given for a correct trial and zero point are given for incorrect trails. Administration was discontinued after three consecutive incorrect trials. The sum of correct trials then used to calculate the scaled score for Arithmetic. The WMI score was then calculated by summing the scaled scores for Digit Span and Arithmetic, which was then age corrected.

Imaging Preprocessing and Analyses

Neurocognitive data were collected on a Siemens 3T Trio magnetic resonance imaging (MRI) scanner at the Center for Cognitive and Behavioral Brain Imaging housed in the Department of Psychology at The Ohio State University. The sequences during this 60-minute imaging session included a high-resolution 3D anatomical T1-weighted structural image using Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE), a T2-weighted Fluid Attenuated Recovery Sequence (FLAIR), and functional T2*-weighted echo planar imaging (EPI) sequences that were collected during the emotion regulation task. The structural MPRAGE volumes were acquired with 176 interleaved axial slices, collected in ascending fashion parallel to the anterior and posterior commissures (1-mm isotropic voxels, 1-mm slice thickness, TR = 1950 ms, TE = 4.44 ms, TI = 950 ms, FOV = 256 mm, flip angle = 12 degrees). An interleaved T2-weighted Fluid Attenuated Recovery Sequence was collected also in anterior to posterior ascending fashion (FLAIR: 2.00-mm slice thickness, # of slices = 60, TR = 14000 ms, TE = 7.3 ms, TI = 2600 ms, flip angle = 120 degrees, 0.8 x 0.8 x 2.0 mm voxel size). A total of 102 volumes were acquired for the emotion regulation task, across three separate runs of the task. These volumes were T2* weighted images, acquired using a fast echo-planar imaging (EPI) sequence (3.4-mm slice thickness, # of slices = 34 per run, TR = 2000 ms, TE = 30 ms, flip angle = 73 degrees).

Lesions were identified manually between two raters to ensure reliability. Any discrepancies were discussed and finalized. Lesions were masked during two steps of the analysis. First, lesions were masked from the structural MPRAGE images to avoid interference with registration; lesions were filled with intensity values consistent with the surrounding voxels. Second, individual lesion masks were included as voxel-dependent variables to mask those regions from the contrasts of interest at the higher-level analysis.

Analysis of imaging data was conducted using fMRIB's software library (FSL; Smith et al., 2004). Data were preprocessed according to an analysis pipeline that included motion correction, slice timing correction, brain extraction, spatial smoothing, temporal filtering, and spatial registration. More specifically, motion correction was done using FMRIB's Linear Registration Tool (MCFLIRT, Jenkinson, Bannister, Brady, & Smith, 2002), which uses a default registration of each volume to the center, to search for volume displacement. Interleaved slice-timing correction was also performed by FSL to correct each voxel's acquisition time. In reality, each slice is acquired at slightly different times, but the slice timing correction changes the time-series so that the rest of the processing assumes that all slices were taken exactly halfway through each volume's acquisition time. Brain extraction was completed using FSL's Brain Extraction Tool (BET, Smith, 2002) to remove the skull. Spatial smoothing was based on a 5-mm Gaussian kernel. A 0.01 Hz (100 second) high temporal filter cutoff was used to remove any low frequency noise due to scanner drift. To correct for individual anatomical location, each participant's functional image was first registered to their lesion-masked T1-weighted MPRAGE. This was followed by a second registration to the Montreal Neurological Institute (MNI) template space. A nonlinear transformation was used for all registrations to optimize for any irregularities in brain structure differences of PwMS. The final product was each individual's functional data registered to standard space to allow for standardized analyses of a neural activation across the sample.

First-level analysis was carried out for each participant on this preprocessed data using fMRIB's expert analysis tool (FEAT; Woolrich, Ripley, Brady, & Smith, 2001). This resulted in voxel-wise parameter estimate maps of the brain for each condition (neutral observe; affect observe; affect regulate). Two contrasts were modeled based on these conditions. The first contrast was Affect Observe > Neutral Observe to explore the differences in neural activation while viewing

negative versus neutral health related images (Aim 1). The other contrast was Affect regulate > Affect Observe to examine the neural differences during reappraisal versus observation of negative health-related images (Aim 2). Given that each participant completed three separate runs of the emotion regulation task, a second-level fixed effects analysis was completed to average each participant's data from each run into one session. FEAT was employed again to compare the activation maps at the group level from each participant's session file for the established conditions (AR; AO; NO) and contrasts (AO>NO; AR>AO). In this analysis of group effects, voxel-wise maps of lesion location were included as a covariate. The analysis yielding group level functional z-stat maps that were cluster thresholded at $z = 2.33$ and $p < .05$.

After examining the outputs created by fMRIB's analysis tool, peak activation within significant clusters were identified in the two contrasts to specify regions of interest (ROIs). Within the AR > AO contrast, we chose an ROI of the dorsolateral prefrontal cortex (dlPFC) because of its association with successful cognitive reappraisal (Buhle et al., 2013; Etkin, Büchel, & Gross, 2015) and its aid in providing cognitive resources for cognitively demanding tasks (Golkar et al., 2012), such as reappraisal. We then created a 12-mm sphere centered around X = 69 mm, Y = 62 mm, Z = 60 mm that included the peak activation of the left dlPFC to extract percent signal change for each contrast from each participant's registered functional data.

Before examining correlations of the dependent variables, all data were assessed for normality, outliers, and errors. Raw data was converted into z-standardized scores. Outliers were identified as greater or equal to 2.5 standard deviations from the sample mean. Scores greater or less than 2.5 standard deviations were corrected and normalized. This calculation was necessary for one participant's reappraisal success score. After these corrections, our main variables of interest were normally distributed; therefore, bivariate correlations were assessed via two-tailed Pearson's *r,*

with significance based on $p<.05$. Percent signal change was correlated with reappraisal success scores and Working Memory Index scores to examine the relationship between behavioral performance on the emotion regulation task, neural recruitment or suppression during a cognitively demanding task, and individual cognitive capacity.

Results

Behavioral Responses to Emotion Regulation Task

Behavioral analyses were conducted to examine negative affect to the health-related images. Aim 1 explored the differences in ratings between negative versus neutral images, whereas Aim 2 examined the differences between reappraisal versus simply observing the negative images. Means and standard error bars for negativity ratings for each condition of the emotion regulation task are presented in Figure 2. A one-way ANOVA (Figure 2) was conducted to compare negativity ratings for the three conditions of the emotion regulation task: neutral observe, affect observe, and affect regulate. The ANOVA showed a main effect of condition ($F(35) = 938.69$, $p < 0.001$; Figure 2). A pairwise comparison was performed with a Bonferroni correction for adjustment of multiple comparisons. The results showed that the mean negativity ratings were significantly lower for the Neutral Observe ($M = 1.07$; $SD = 0.19$) compared to the Affect Observe condition ($M = 1.97$; $SD = 0.54$; $p < 0.001$; Figure 2). Negativity ratings were also significantly lower during the Affect Regulate ($M = 1.67$; $SD = 0.38$) condition than the Affect Observe condition ($M = 1.97$; $SD = 0.54$; $p < 0.001$; Figure 2).

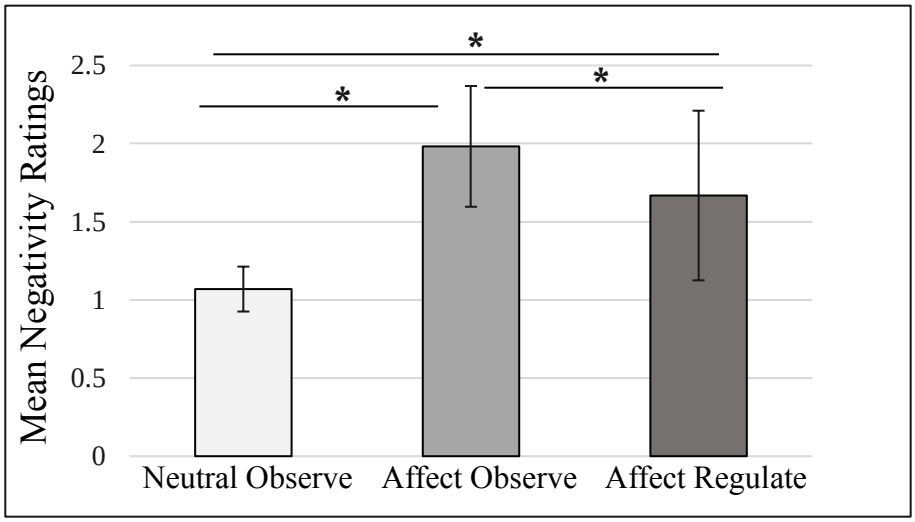

Figure 2. Bar graph showing the comparison of mean negativity ratings during the MRI emotion regulation task for the three conditions: Neutral Observe, Affect Observe, and Affect Regulate.

Neural Responses to Negative Versus Neutral Images

We next explored the neural differences while observing negative versus neutral health-related images. We hypothesized increased activity in emotion generating regions, like the amygdala, while viewing negative compared to neutral images. In the AO > NO contrast, there was no significant difference in activation of the amygdala (Figure 3). Additionally, participants were less successful at deactivating regions of the default mode network (DMN); a network of regions that is usually suppressed during an active task (Greicius, Krasnow, Reiss, & Menon, 2002). Specifically, the precuneus as well as anterior and posterior areas of the dorsal cingulate cortex, were less deactivated in the contrast of AO>NO (Table 3; Figure 3). Interestingly, we also observed greater activity in the posterior portion of the dorsal cingulate cortex as well as the middle frontal gyrus and left frontal pole in the AO>NO contrast there were regions that were not less suppressed, but more active during AO > NO. Some posterior portions of the dorsal cingulate cortex as well as the middle frontal gyrus and left frontal pole were significantly activated during this condition (Figures 3 & 4).

Table 3. Cortical regions activated or deactivated during the Affect Observe > Neutral Observe contrast.

Contrast	Anatomical Region	Max z-stat	MNI coordinates (mm)		
			X	Y	Z
AO>NO	Posterior cingulate gyrus	5.75	0	-36	30
AO>NO	Precuneus cortex	5.64	-10	-72	46
AO>NO	Superior parietal lobe	5.54	-36	-50	48
AO>NO	Lateral superior occipital cortex	5.4	-24	-70	54
AO>NO	Anterior supramarginal gyrus	4.68	-56	-34	46
AO>NO	Middle frontal gyrus	4.29	-40	36	34
AO>NO	Frontal pole	3.8	-42	46	8
AO>NO	Middle frontal gyrus	3.53	-26	-2	56

AO>NO	Anterior cingulate gyrus	2.53	-4	-14	36

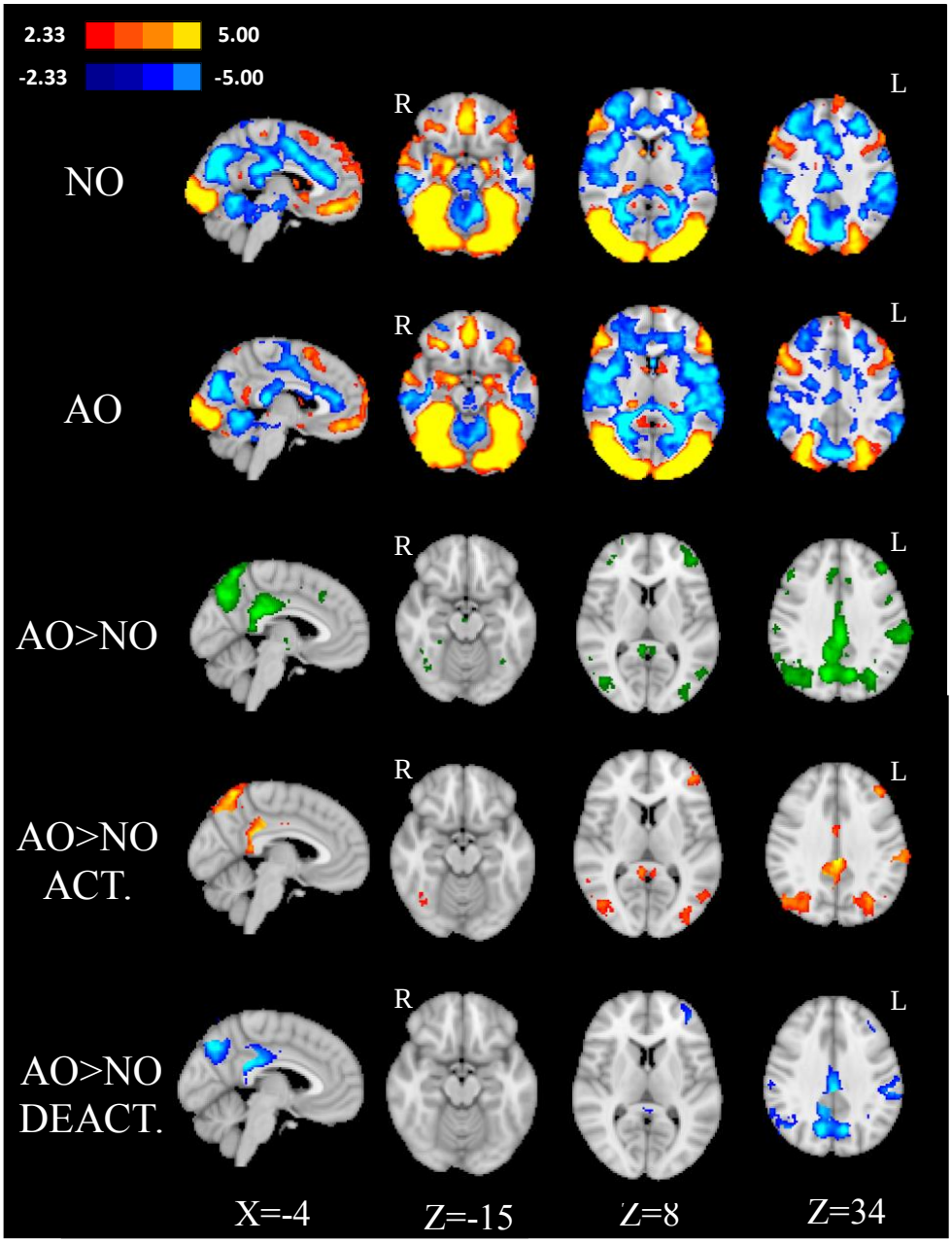

Figure 3. Cortical activation and deactivation in the Neutral Observe (NO) and Affect Observe (AO) conditions. All significant differences in cortical recruitment (green) are shown in the third row for the AO > NO contrast. Only significant differences in which there was activation during AO (red-yellow) are shown in the fourth row. Finally, only significant differences in which there was less deactivation in AO than NO (blue-light blue) are shown in the fifth row.

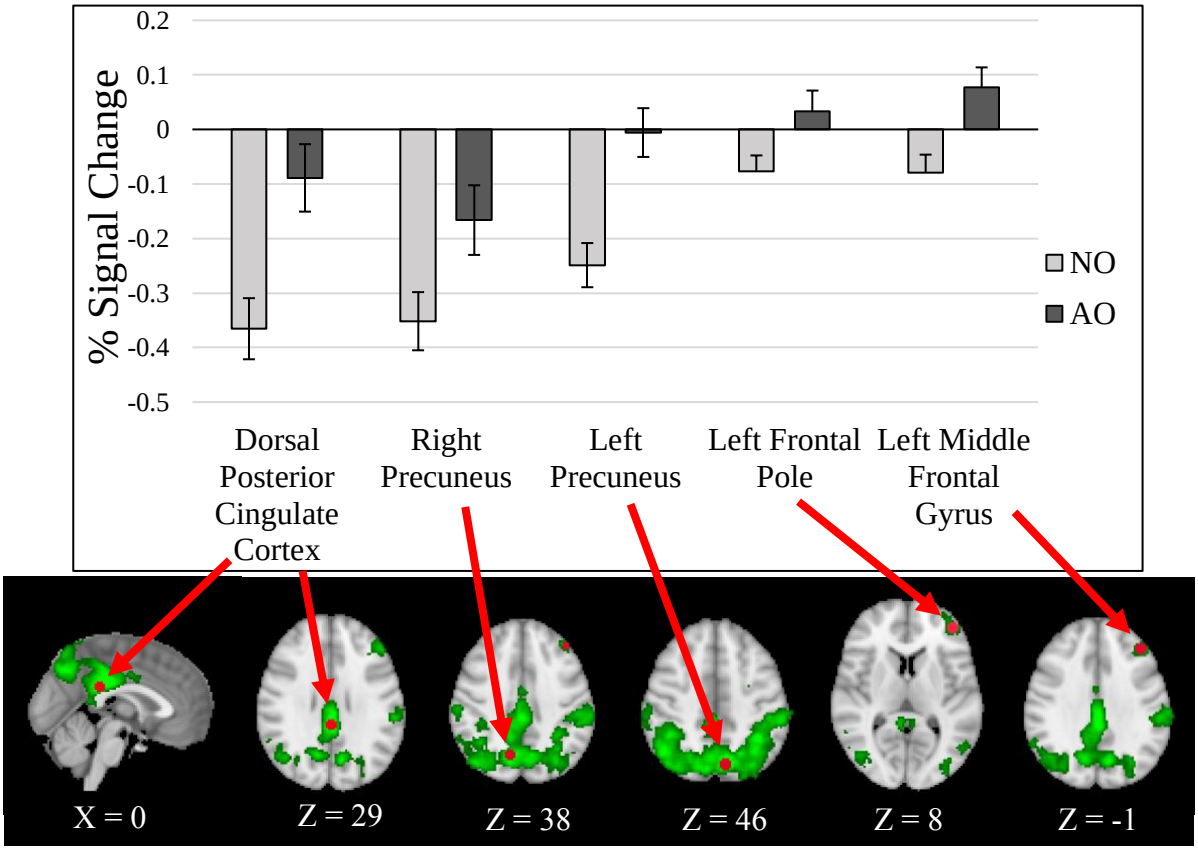

Figure 4. Bar graph showing significant activation or deactivation of five example regions within the Affect Observe > Neutral Observe (AO > NO) contrast. Accompanied by cortical recruitment images displaying all significant differences in recruitment (green) with a highlight of each ROI (red) during the AO > NO contrast.

Neural Responses During Reappraisal Versus Observe

We then examined differences in neural activation and deactivation during the use of reappraisal versus viewing of negative health-related images. We hypothesized greater recruitment of executive control regions while participants were instructed to use reappraisal than observe. Within the AR > AO contrast, as hypothesized, we observed significant activation of executive control regions, such as the dorsolateral PFC and bilateral middle frontal gyri, (Figures 5 and 6). Additionally, we also observed increased activity in the anterior cingulate cortex and the posterior cingulate cortex in AR>AO contrast. However, participants did not show significantly less amygdala activity in the AR > AO contrast (Figure 5).

Table 4. Cortical regions activated or deactivated during the Affect Regulate > Affect Observe contrast.

Contrast	Anatomical Region	Max z-stat	MNI coordinates (mm)		
			X	Y	Z
AR>AO	Lingual gyrus	5.20	-8	-58	0
AR>AO	Left dorsolateral prefrontal cortex	4.69	-48	-2	50
AR>AO	Superior middle temporal gyrus	4.67	50	-32	2
AR>AO	Precuneus	4.59	-8	-62	16
AR>AO	Right dorsolateral prefrontal cortex	4.5	54	-2	44
AR>AO	Medial frontal cortex	3.52	-12	44	-10
AR>AO	Anterior cingulate cortex	3.14	-2	30	-8

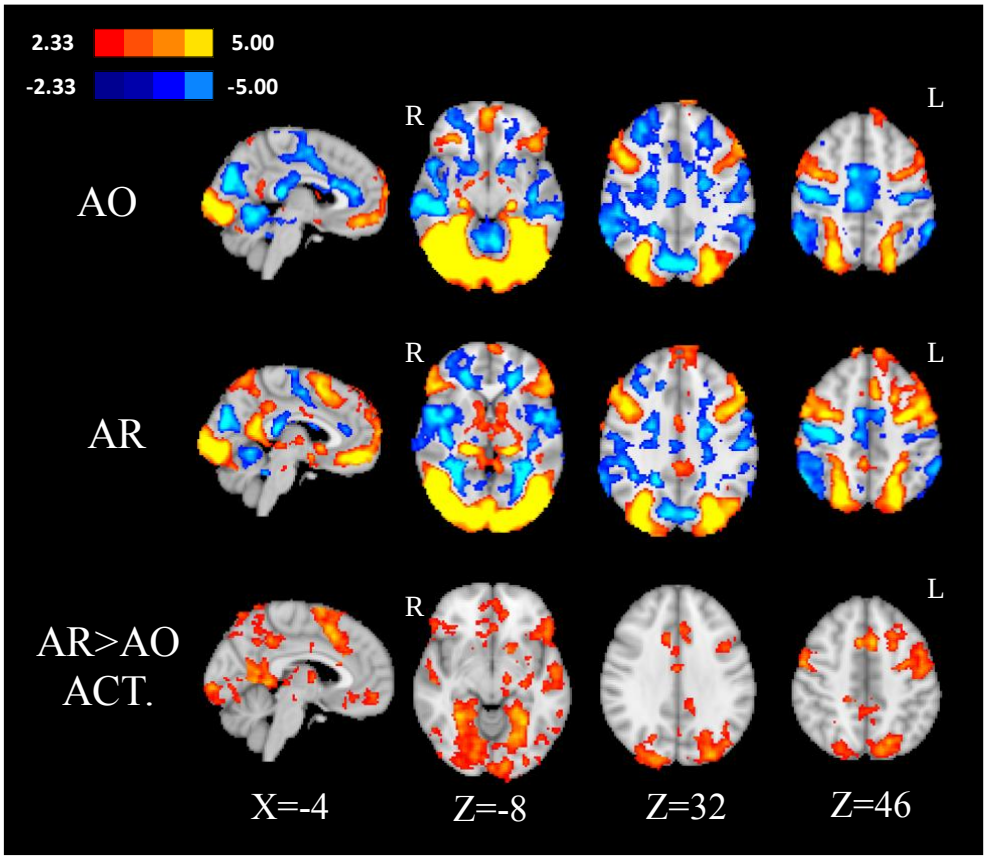

Figure 5. Cortical activation and deactivation in the Affect Observe (AO) and Affect Regulate (AR) conditions. All significant differences in cortical recruitment (green) are shown in the third row for the AR > AO contrast. Only significant differences in which there was activation during AR (red-yellow) are shown in the fourth row. There were no regions exhibiting less deactivation in this contrast.

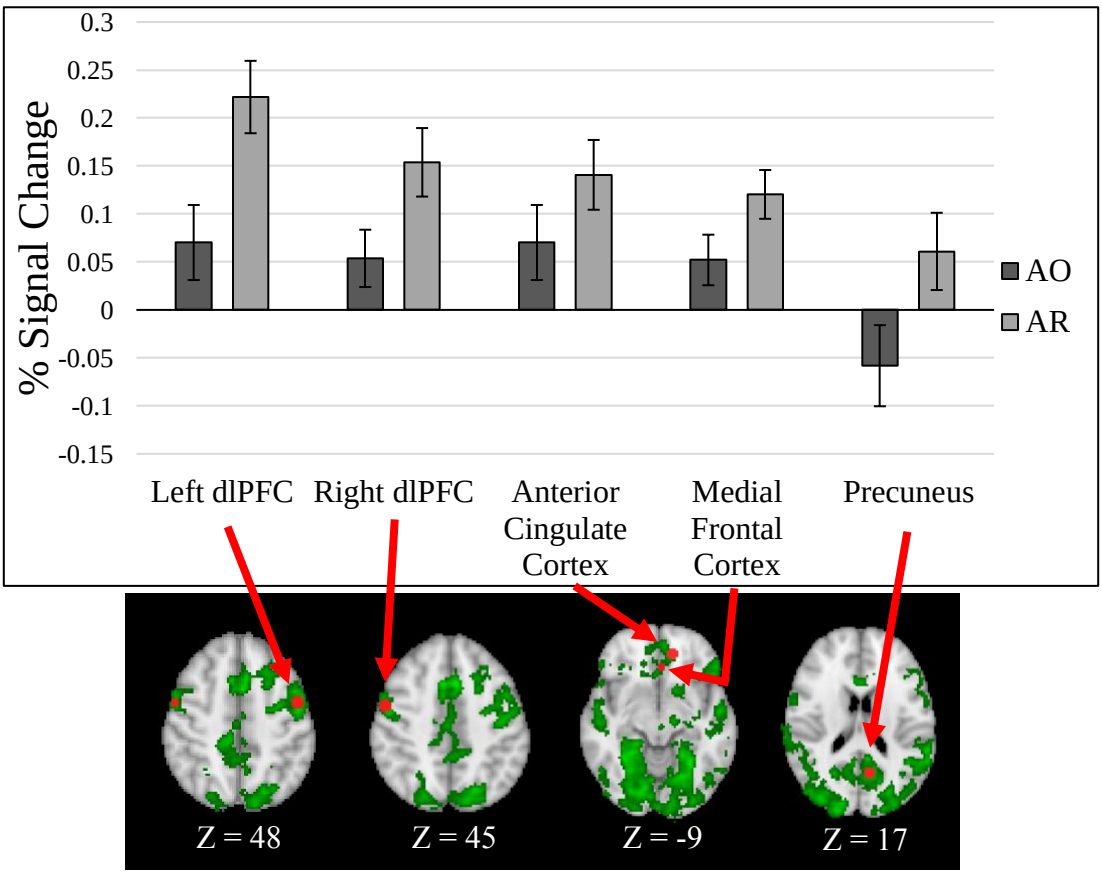

Figure 6. Bar graph showing significant activation or deactivation of five example region within the Affect Regulate > Affect Observe (AR > AO) contrast. Accompanied by cortical recruitment images displaying all significant differences in recruitment (green) with a highlight of each ROI (red) during the AR > AO contrast.

Associations of Behavioral and Neural Correlates of ER with Cognitive Capacity

The final analyses evaluated the degree to which cognitive capacity was related to behavioral and neural correlates of emotion regulation ability. Given the involvement of the dorso-lateral prefrontal cortices (dlPFC) in emotion regulation, we examined whether cognitive capacity, indexed via Working Memory Index, was associated with neural activity in the DLPFC during the AR>AO contrast. Percent signal change within the left dlPFC ROI was thus extracted. Interestingly, high Working Memory Index was associated with greater recruitment of the left dlPFC during reappraisal ($r = 0.326$, $p = .046$; Figure 7); with higher dlPFC activity additionally

associated with greater reappraisal success (r = 0.384, p = .017; Figure 8). There was no significant relationship between Working Memory Index and reappraisal success (r = 0.234, p = .157; Table 5).

Table 5. Correlations between cognitive capacity, reappraisal success, and neural recruitment during reappraisal.

	1	2	3
1. Working Memory Index	--		
2. Reappraisal Success	.234	--	
3. dlPFC (AR>AO)	.326*	.384*	--

Note: dlPFC = dorsolateral prefrontal cortex; AR = Affect Regulate condition; AO = Affect Observe condition.
*$p < .05$, two-tailed.
[a]n = 38.

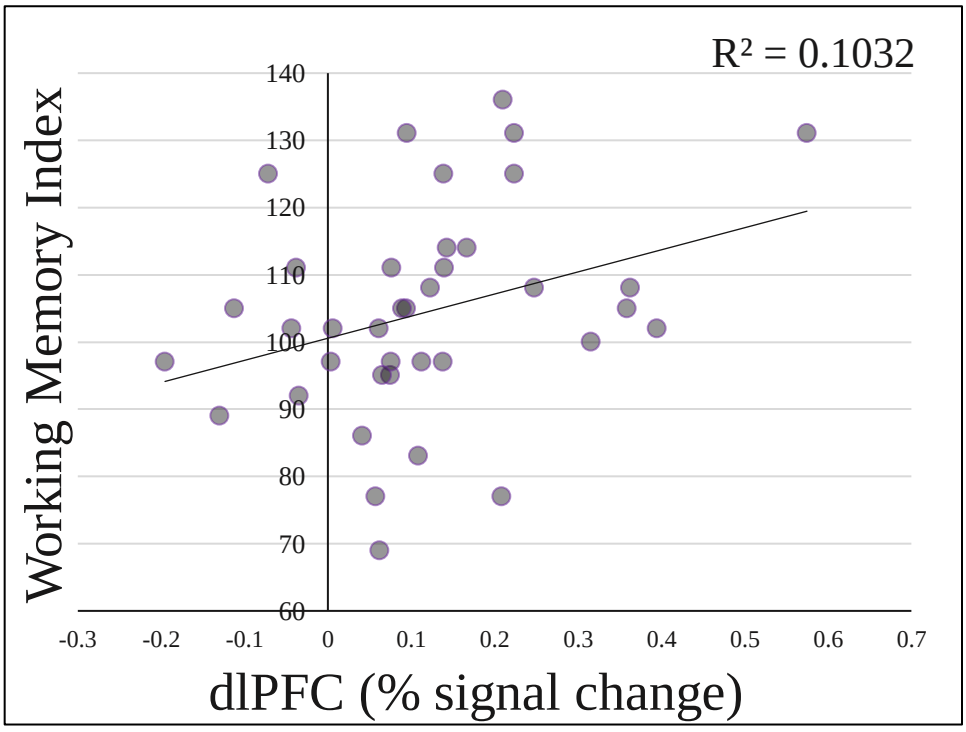

Figure 7. Association between the WAIS-IV Working Memory Index scores and percent signal change of the dorsolateral prefrontal cortex (dlPFC) in the AR > AO contrast.

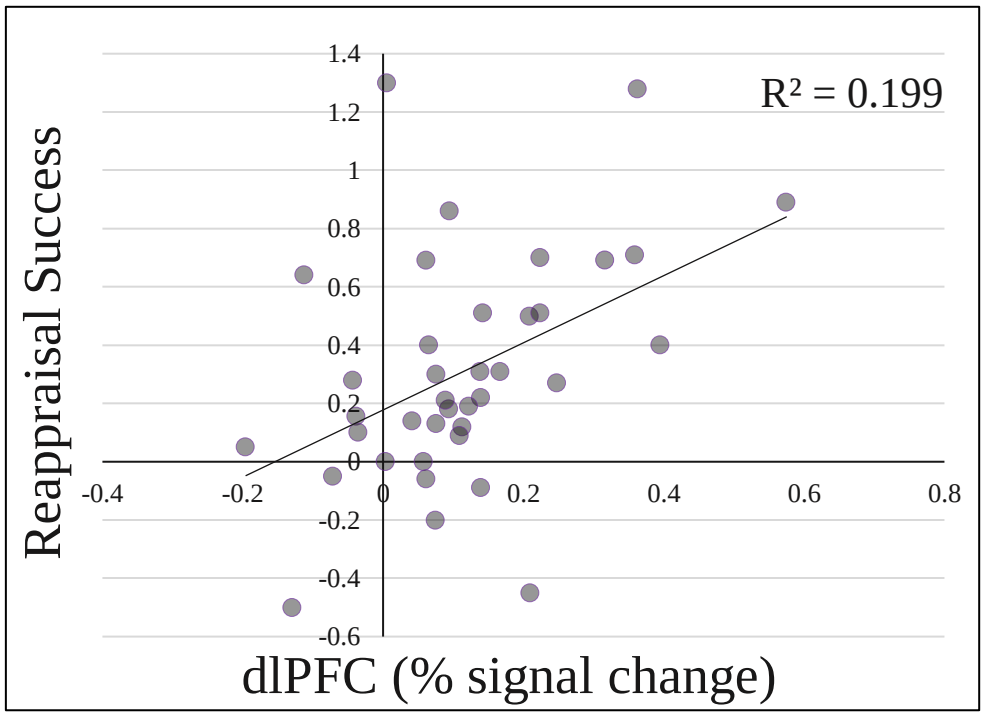

Figure 8. Association between reappraisal success (mean negativity ratings of AR – AO) and percent signal change of the dorsolateral prefrontal cortex (dlPFC) in the AR > AO contrast.

Discussion

Despite the high prevalence of MS and its known impact on psychiatric disturbances (see Chwastiak & Ehde, 2007 for review), there is limited research aimed at understanding the behavioral and neural correlates of difficulties with emotion regulation in this population. As such, the goal of this study was to explore the relationship between cognitive capacity and cognitive reappraisal at both the behavioral and neural levels, to understand the possible role that deficits in cognitive functioning may have on affective functioning in individuals with MS. Our results suggest that cognitive reappraisal is a cognitively demanding strategy, requiring recruitment of executive control regions, like the dlPFC. The results also provide evidence that deficits in working memory capacity may limit how individuals with chronic illnesses, such as MS, can regulate their emotional experiences by showing that these two processes are closely related.

In this study, we first examined the behavioral and neural responses to a novel set of neutral and negative health-related images. Behaviorally, participants reported significantly higher negativity ratings while viewing negative compared to neutral images. This validated the manipulation of the images, meaning the negative health-related images successfully elicited negatively valanced emotions. Neurally, we expected to find an increase in activation of emotion generating regions, such as the amygdala, while viewing negative compared to neutral images. Amygdala activation did not come out significant in this contrast; however, when we explored activation in the individual conditions, affect observe and neutral observe, we found that the effect was in the expected direction. Additionally, the contrast of AO>NO also showed activation in regions of the default-mode network (DMN). This network of regions is thought to contribute to emotion generation and regulation through an internal mentation process by creating mental

representations of present experiences or stimuli based on representations of previous experiences (Barrett and Satpute, 2013). The DMN, comprising of the precuneus, posterior cingulate cortex (PCC) and ventral anterior cingulate cortex (vACC), has been found to be suppressed during active cognitive tasks (Prakash et al., 2012). While the dorsal PCC and the precuneus, bilaterally, were suppressed while participants were engaged in viewing of both negative and neutral stimuli, these regions were significantly less suppressed while viewing negative images compared to neutral images. These results suggest that negative images may have elicited internal self-referential mentation due to the relevance of the health-related images to participants' experiences with chronic illness.

Interestingly, some areas of the cingulate cortex, the left frontal pole, and middle frontal gyrus were not less suppressed but were significantly activated while viewing negative images. It is possible that the negative health-related images elicited such an internal mentation response that some regions showed increased activity. This is consistent with a study that explored the neural functioning of the DMN and found that some areas, specifically the precuneus and PCC, were thought to be transiently active (Raichle et al, 2001), suggesting that these areas play an integral role in switching between activation and suppression depending on the stimuli and/or the goal-directed task being performed. In line with this hypothesis, Passamonti et al. 2009 reported greater activity in the precuneus in PwMS compared to healthy adults while viewing emotionally-eliciting stimuli compared to neutral stimuli (Passamonti et al., 2009). These results aid in understanding the complex recruitment of the DMN in PwMS by showing that some regions remain suppressed while some become more active in the context of processing negatively valanced stimuli.

The second aim was to examine the differences between using cognitive reappraisal versus observation while viewing negative health-related stimuli at the behavioral and neural levels. Behaviorally, participants reported significantly lower negative ratings while using cognitive reappraisal versus simply viewing the negative images, suggesting that participants were successful in downregulating their negative emotional responses, via cognitive reappraisal, to the images. There is recent work exploring emotion regulation abilities in PwMS versus healthy adults, which found that there is no difference in emotion regulation success in PwMS compared to healthy controls (Prakash et al., under review). Our results found that PwMS were able to downregulate their emotional experiences successfully, however, there was no healthy control group with which to compare. Neurally, successful use of cognitive reappraisal resulted in significant activation of executive functioning regions, such as the bilateral dorsolateral prefrontal cortices, and the middle frontal gyrus. These results suggest that cognitive reappraisal is a cognitively demanding strategy, requiring more recruitment of these executive control regions in order to regulate successfully. This is consistent with a meta-analysis that found an increase in executive functioning regions, specifically the prefrontal cortex, in response to challenging cerebral tasks (Hillary et al., 2006), meaning that greater recruitment of the prefrontal cortex is integral for successful performance of cognitive demanding tasks, such as cognitive reappraisal.

Interestingly, there was also significant activation in the anterior cingulate cortex (ACC) and areas of the DMN, specifically the precuneus, during reappraisal versus observation. This is consistent with literature finding greater activation in the DMN during successful reappraisal in healthy adults (Xie et al., 2016). Less DMN suppression also has been shown to allow for more cognitive control recruitment (Vanderhasselt et al., 2013), resulting in greater success during

cognitively demanding tasks, such as reappraisal. There is also literature exhibiting that more recruitment of the ACC is correlated with effective reappraisal (Botvinick et al., 2001). Both the prefrontal cortex and the ACC have been found to be significantly activated during reappraisal of negative emotions as well as cognitive control processes (Oschner & Gross, 2005). Consistent with previous research highlighting the similarities of the neural systems underlying cognitive control and emotion regulation (Gross, 2002; Oschner & Barrett, 2001), these results contribute to the growing understanding that the two processes are closely connected and interdependent.

The final aim of the study was to further explore this relation by examining the role of cognitive capacity in emotion regulation performance in MS. There was a positive association between an executive functioning region, the dlPFC and reappraisal success, suggesting that those who recruited the dlPFC more were more successful at downregulating their negative emotions. This validates that this region plays an important role in emotion regulation ability, consistent with previous work done on emotion regulation in healthy adults (Golkar et al., 2012). There was also a significant positive correlation between dlPFC recruitment and WMI scores, suggesting that those with greater cognitive capacity, measured through working memory, were the ones who were recruiting this region more that is important for emotion regulation success. This is consistent with previous work that has found that prefrontal cortex recruitment is directly proportionate of the difficulty of a task (Hillary et al., 2006), and in turn, the amount of cognitive capacity required to perform the task. These results continue to build upon the growing literature that cognitive functioning and cognitive reappraisal involve very similar behavioral and neural processes. Conceptualizing these results will aid in the understanding of affective functioning in MS by showing that cognitive deficits may limit how well individuals can regulate their emotional experiences.

Due to these two expected relationships being significant, we predicted that WMI would also be positively correlated with reappraisal success. However, WMI scores were not significantly correlated with reappraisal success, which was not consistent with our hypothesis or previous literature that has found this relationship (Schmeichel, Volokhov, & Demaree, 2008), although the correlation was marginally significant and in the expected direction. One potential factor limiting our ability to observe this association may have been a restricted range of cognitive capacity. Our sample had WMI scores that were rather close to the normative distribution (M = 104.34; SD = 15.76) with only four out of 38 participants falling below one standard deviation from the mean (i.e., < 85). During recruitment, the sample was restricted to a relatively low disease severity in which participants retained some mobility (*EDSS range* = 0 - 5.5), given that other aims of this study were directed at investigating physical activity levels. However, this restricted range of disease severity may have contributed to a more cognitively intact sample, and it is possible that the relationship between WMI and cognitive reappraisal would be stronger in a sample with a larger representation of cognitive deficits. For example, one study found relationships between many domains of executive functioning, including working memory and emotion regulation, in a chronic illness population but not in healthy controls (Campbell et al., 2009).

There are a few other limitations that are important to note while interpreting the results of this study. One limitation is that the current study explored only one measure of cognitive performance: working memory capacity. Declines in other measures of cognitive function, such as processing speed, have also been shown to contribute to higher levels of affective symptoms in this population (Phillips et al., 2014), so future studies should explore beyond working memory. Another main limitation is the lack of a healthy control sample to compare to the MS

participants. Unlike studies that have a controlled comparison group, we are unable to speak to differences in the effects of cognitive deficits on affective symptoms between the MS and healthy populations. Thus, our conclusions are limited to individual differences of cognitive capacity and emotion regulation ability within the sample of PwMS. Further research in this area could include healthy controls in order to make more externally valid claims regarding the effects of MS-related declines in cognitive performance on emotion regulation. Yet another limitation is that the current study was a cross sectional design, which inhibits our ability to make claims suggesting causality. Therefore, we are not able to speak to whether cognitive capacity influences successful employment of emotion regulation strategies or whether it is the difficulty in emotion regulation that additionally impacts cognitive control. However, the results of this cross-sectional study could inform a more complex longitudinal design in future studies to explore how these relationships continue or change over time.

The present study highlights the relationship between cognitive functioning and emotion regulation ability within PwMS. Although the interaction is not completely understood, this study underscores how cognitive deficits, prevalent in about 40-50% of the population (Rao, Leo, Bernardin, Unverzagt, 1991; Bobholz & Rao, 2003), may play a central role in the extent to which PwMS are able to perform cognitive demanding tasks, such as reappraisal. These results continue the increasing understanding that there is a great amount of overlap in the behavioral and neural processes of cognitive control and emotion regulation. Future research could capitalize upon these interdependent processes by exploring how interventions that are aimed at improving cognitive function, such as mindfulness-based stress reduction interventions, might improve emotion regulation abilities in PwMS.

References

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical Psychology Review,* 30(2), 217-237. doi:10.1016/j.cpr.2009.11.004

Amato, M. P. (1995). Cognitive Impairment in Early-Onset Multiple Sclerosis. *Archives of Neurology,52*(2), 168. doi:10.1001/archneur.1995.00540260072019

Arnett, P. A., Meyer, J. E., Merritt, V. C., & Strober, L. B. (2018). Multiple Sclerosis and Related Disorders. In J. E. Morgan & J. H. Ricker (Eds.), *Textbook of clinical neuropsychology* (pp. 581-638). New York, NY: Routledge.

Barrett, L. F., & Satpute, A. B. (2013). Large-scale brain networks in affective and social neuroscience: Towards an integrative functional architecture of the brain. *Current Opinion in Neurobiology, 23*(3), 361-372. doi:10.1016/j.conb.2012.12.012

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for The Beck Depression Inventory-II. San Antonio, TX: Psychological Corp.

Bobholz, J. A., & Rao, S. M. (2003). Cognitive dysfunction in multiple sclerosis: A review of recent developments. *Current Opinion in Neurology, 16*(3), 283-288. doi:10.1097/00019052-200306000-00006

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108*(3), 624-652. doi:10.1037/0033-295x.108.3.624

Brownell, B., & Hughes, J. T. (1962). The distribution of plaques in the cerebrum in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry,* 25(4), 315-320. doi:10.1136/jnnp.25.4.315

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., . . . Ochsner, K. N. (2013). Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. *Cerebral Cortex*, 24(11), 2981-2990. doi:10.1093/cercor/bht154

Calabrese, P. (2006). Neuropsychology of multiple sclerosis. *Journal of Neurology, 253*(S1), I10-I15. doi:10.1007/s00415-006-1103-1

Campbell, L.K., Scaduto, M., Van Slyke, D., Niarhos, F., Whitlock, J.A., & Compas, B.E. (2009). Executive function, coping, and behavior in survivors of childhood acute lymphocytic leukemia. *Journal of Pediatric Psychology*, 34, 317327.

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurology, 7*(12), 1139-1151.

Chiaravalloti, N. D., Hillary, F. G., Ricker, J. H., Christodoulou, C., Kalnin, A. J., Liu, W., . . . Deluca, J. (2005). Cerebral Activation Patterns During Working Memory Performance in Multiple Sclerosis Using fMRI. *Journal of Clinical and Experimental Neuropsychology, 27*(1), 33-54. doi:10.1080/138033990513609

Chwastiak, L. A., & Ehde, D. M. (2007). Psychiatric Issues in Multiple Sclerosis. *Psychiatric Clinics of North America, 30*(4), 803-817. doi:10.1016/j.psc.2007.07.003

Conway, A. R., Kane, M. J., Bunting, M. F., Hambrick, D. Z., Wilhelm, O., & Engle, R. W. (2005). Working memory span tasks: A methodological review and user's guide. *Psychonomic Bulletin & Review, 12*(5), 769-786. doi:10.3758/bf03196772

Dennison, L., Moss-Morris, R., & Chalder, T. (2009). A review of psychological correlates of adjustment in patients with multiple sclerosis. *Clinical Psychology Review, 29*(2), 141-153. doi:10.1016/j.cpr.2008.12.001

Diamond, B., Johnson, S., Kaufman, M., & Graves, L. (2008). Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. *Archives of Clinical Neuropsychology, 23*(2), 189-199. doi:10.1016/j.acn.2007.10.002

Etkin, A., Büchel, C., & Gross, J. J. (2015). The neural bases of emotion regulation. *Nature Reviews Neuroscience, 16*(11), 693-700. doi:10.1038/nrn4044

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189-198. doi:https://doi.org/10.1016/0022-3956(75)90026-6

Gennari, S. P., Millman, R. E., Hymers, M., & Mattys, S. L. (2018). Anterior paracingulate and cingulate cortex mediates the effects of cognitive load on speech sound discrimination. *NeuroImage, 178*, 735-743. doi:10.1016/j.neuroimage.2018.06.035

Goldin, P. R., Mcrae, K., Ramel, W., & Gross, J. J. (2008). The Neural Bases of Emotion Regulation: Reappraisal and Suppression of Negative Emotion. *Biological Psychiatry*, 63(6), 577-586. doi:10.1016/j.biopsych.2007.05.031

Golkar, A., Lonsdorf, T. B., Olsson, A., Lindstrom, K. M., Berrebi, J., Fransson, P., . . . Öhman, A. (2012). Distinct Contributions of the Dorsolateral Prefrontal and Orbitofrontal Cortex during Emotion Regulation. *PLoS ONE, 7*(11). doi:10.1371/journal.pone.0048107

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2002). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences, 100*(1), 253-258. doi:10.1073/pnas.0135058100

Gross, J. J. (1998). The emerging field of emotion regulation: An integrative review. *Review of General Psychology*, 2(3), 271-299. doi:10.1037//1089-2680.2.3.271

Gross, J. J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology, 39*(3), 281-291. http://dx.doi.org.proxy.lib.ohio-state.edu/10.1017/S0048577201393198

Gross, J. J. (2013). Emotion regulation: Taking stock and moving forward. *Emotion, 13*(3), 359-365. doi:10.1037/a0032135

Gross, J. J., & Barrett, L. F. (2011). Emotion generation and emotion regulation: One or two depends on your point of view. *Emotion Review*, 3, 8 –16. doi:10.1177/1754073910380974

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology, 85*(2), 348-362. doi:10.1037/0022-3514.85.2.348

Gross, J. J., & Thompson, R. A. (2007). Emotion regulation: Conceptual foundations. In J. J. Gross (Ed.), Handbook of emotion regulation (pp. 3–24). New York, NY: Guilford Press.

Gross, J. J., Sheppes, G., & Urry, H. L. (2011). Emotion generation and emotion regulation: A distinction we should make (carefully*). Cognition and Emotion*, 25, 765–781. doi:10.1080/02699931.2011.555753

Hillary, F. G., Genova, H. M., Chiaravalloti, N. D., Rypma, B., & Deluca, J. (2006). Prefrontal modulation of working memory performance in brain injury and disease. *Human Brain Mapping,27*(11), 837-847. doi:10.1002/hbm.20226

Hillary, F., Chiaravalloti, N., Ricker, J., Steffener, J., Bly, B., Lange, G., . . . Deluca, J. (2003). An Investigation of Working Memory Rehearsal in Multiple Sclerosis Using fMRI. *Journal of Clinical and Experimental Neuropsychology, 25*(7), 965-978. doi:10.1076/jcen.25.7.965.16490

Jenkinson, M., Bannister, P., Brady, J. M. and Smith, S. M. (2002) Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage, 17*(2), 825-841.

John, O. P., & Gross, J. J. (2004). Healthy and unhealthy emotion regulation: Personality processes, individual differences, and lifespan development. Journal of Personality, 72, 1301–1333. doi:10.1111/j.1467- 6494.2004.00298.x

Kappas, A. (2011). Emotion and regulation are one! *Emotion Review*, 3, 17–25. doi:10.1177/1754073910380971

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology, 33*(11), 1444-1444. doi:10.1212/wnl.33.11.1444

Mesquita, B., & Frijda, N. H. (2011). An emotion perspective on emotion regulation. Cognition and Emotion, 25, 782–784. doi:10.1080/02699931.2011.586824

Multiple Sclerosis FAQs. (2017). Retrieved from https://www.nationalmssociety.org/What-is-MS/MS-FAQ-s#question-What-is-multiple-sclerosis

Ochsner, K. N., & Barrett, L. F. (2001). A multiprocess perspective on the neuroscience of emotion. In T. J. Mayne & G. A. Bonanno (Eds.), *Emotions and social behavior. Emotions: Currrent issues and future directions* (pp. 38-81). New York, NY, US: Guilford Press.

Ochsner, K. N., & Gross, J. J. (2008). Cognitive Emotion Regulation: Insights from Social Cognitive and Affective Neuroscience. *Current Directions in Psychological Science, 17*(2), 153-158. doi:10.1111/j.1467-8721.2008.00566

Ochsner, K., & Gross, J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences, 9*(5), 242-249. doi:10.1016/j.tics.2005.03.010

Opitz, P. C., Gross, J. J., & Urry, H. L. (2012). Selection, Optimization, and Compensation in the Domain of Emotion Regulation: Applications to Adolescence, Older Age, and Major Depressive Disorder. Social and Personality Psychology Compass, 6(2), 142-155. doi:10.1111/j.1751-9004.2011.00413

Parmenter, B. A., Shucard, J. L., Benedict, R. H., & Shucard, D. W. (2006). Working memory deficits in multiple sclerosis: Comparison between the n-back task and the Paced Auditory Serial Addition Test. *Journal of the International Neuropsychological Society, 12*(05). doi:10.1017/s1355617706060826

Passamonti, L., Cerasa, A., Liguori, M., Gioia, M. C., Valentino, P., Nistico, R., . . . Fera, F. (2009). Neurobiological mechanisms underlying emotional processing in relapsing-remitting multiple sclerosis. *Brain, 132*(12), 3380-3391. doi:10.1093/brain/awp095

Pe, M. L., Raes, F., & Kuppens, P. (2013). The Cognitive Building Blocks of Emotion Regulation: Ability to Update Working Memory Moderates the Efficacy of Rumination and Reappraisal on Emotion. *PLoS ONE*, 8(7). doi:10.1371/journal.pone.0069071

Phillips, L. H., Henry, J. D., Nouzova, E., Cooper, C., Radlak, B., & Summers, F. (2014). Difficulties with emotion regulation in multiple sclerosis: Links to executive function, mood, and quality of life. *Journal of Clinical and Experimental Neuropsychology*, 36(8), 831-842. doi:10.1080/13803395.2014.946891

Phillips, M. L., Ladouceur, C. D., & Drevets, W. C. (2008). A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry, 13*(9), 833-857. doi:10.1038/mp.2008.65

Phillips, L. H., Saldias, A., Mccarrey, A., Henry, J. D., Scott, C., Summers, F., & Whyte, M. (2009). Attentional lapses, emotional regulation and quality of life in multiple sclerosis. *British Journal of Clinical Psychology*, 48(1), 101-106. doi:10.1348/014466508x379566

Prakash, R. S., Erickson, K. I., Snook, E. M., Colcombe, S. J., Motl, R. W., & Kramer, A. F. (2008). Cortical recruitment during selective attention in multiple sclerosis: An fMRI investigation of individual differences. *Neuropsychologia, 46*(12), 2888-2895. doi:10.1016/j.neuropsychologia.2008.05.027

Prakash, R. S., Heo, S., Voss, M. W., Patterson, B., & Kramer, A. F. (2012). Age-related differences in cortical recruitment and suppression: Implications for cognitive performance. *Behavioural Brain Research*, 230(1), 192-200. doi:10.1016/j.bbr.2012.01.058

Prakash, R. S., Schirda, B., Valentine, T. R., Crotty, M., & Nicholas, J. (in progress). Emotion Dysregulation in Multiple Sclerosis: Impact on Symptoms of Depression and Anxiety.

Prakash, R. S., Snook, E. M., Lewis, J. M., Motl, R. W., & Kramer, A. F. (2008). Cognitive impairments in relapsing-remitting multiple sclerosis: A meta-analysis. *Multiple Sclerosis Journal,14*(9), 1250-1261. doi:10.1177/1352458508095004

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, 98*(2), 676-682.

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis.: I. Frequency, patterns, and prediction. *Neurology, 41*(5), 685-691. doi:10.1212/wnl.41.5.685

Roth, A. K., Denney, D. R., & Lynch, S. G. (2015). Information processing speed and attention in multiple sclerosis: Reconsidering the Attention Network Test (ANT). *Journal of Clinical and Experimental Neuropsychology*, 37(5), 518-529. doi:10.1080/13803395.2015.1037252

Rouleau, I., Dagenais, E., Tremblay, A., Demers, M., Roger, É, Jobin, C., & Duquette, P. (2017). Prospective memory impairment in multiple sclerosis: A review. *The Clinical Neuropsychologist,32*(5), 922-936. doi:10.1080/13854046.2017.1361473

Schirda, B., Nicholas, J. A., & Prakash, R. S. (2015). Examining trait mindfulness, emotion dysregulation, and quality of life in multiple sclerosis. *Health Psychology*, 34(11), 1107-1115. http://dx.doi.org/10.1037/hea0000215

Schmeichel, B. J., & Demaree, H. A. (2010). Working memory capacity and spontaneous emotion regulation: High capacity predicts self-enhancement in response to negative feedback. *Emotion,10*(5), 739-744. doi:10.1037/a0019355

Schmeichel, B. J., Volokhov, R. N., & Demaree, H. A. (2008). Working memory capacity and the self-regulation of emotional expression and experience. *Journal of Personality and Social Psychology, 95*(6), 1526-1540. doi:10.1037/a0013345

Smith, S. M. (2002) Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3):143-155.

Vanderhasselt, M., Baeken, C., Schuerbeek, P. V., Luypaert, R., & Raedt, R. D. (2013). Inter-individual differences in the habitual use of cognitive reappraisal and expressive suppression are associated with variations in prefrontal cognitive control for emotional information: An event related fMRI study. *Biological Psychology*, 92(3), 433-439. doi:10.1016/j.biopsycho.2012.03.005

Vohs, K.D. and Heatherton, T.F. (2000) Self-regulatory failure: a resource-depletion approach. Psychol. Sci. 11, 249–254

Wechsler, D. (2008). WAIS-IV: Administration and scoring manual. New York, NY: The Psychological Corporation.

Wierenga, K. L., Lehto, R. H., & Given, B. (2017). Emotion Regulation in Chronic Disease Populations: An Integrative Review. *Research and Theory for Nursing Practice, 31*(3), 247-271. doi:10.1891/1541-6577.31.3.247

Woolrich, M. W., Behrens, T. E. J., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. NeuroImage, 21(4), 1732–1747. http://doi.org/10.1016/j.neuroimage.2003.12.023

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal Autocorrelation in Univariate Linear Modeling of FMRI Data. NeuroImage, 14(6), 1370–1386. http://doi.org/10.1006/nimg.2001.0931

Xie, X., Bratec, S. M., Schmid, G., Meng, C., Doll, A., Wohlschläger, A., . . . Sorg, C. (2016). How do you make me feel better? Social cognitive emotion regulation and the default mode network. *NeuroImage*, 134, 270-280. doi:10.1016/j.neuroimage.2016.04.015